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Research Article

Effect of vaginal pH on efficacy of dinoprostone gel for labour induction

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ABSTRACT

Background: Induction of labour is defined as an intervention designed to artificially initiate uterine contractions leading to progressive dilatation and effacement of the cervix and birth of the baby. The aim of the study was to evaluate the influence of vaginal pH on the efficacy of dinoprostone gel for labor induction.
Methods: A prospective study conducted on 200 subjects within 1 year in India. The Bishop score and vaginal pH (with pH paper, Sigma Chemical Company, St. Louis, USA) of subjects undergoing induction of labor with dinoprostone gel was assessed prior induction. After 6 hours of induction, PGE2 gel was repeated or labor was augmented. The vaginal pH measured was compared with age, parity, Bishop Score, time to enter into active phase of labor, and the mode of delivery. The significance of association was calculated by Chi-square test.
Results: Majority subjects had pH in the range 5-6.Subjects with higher parity were associated with higher vaginal ph. Higher vaginal pH was associated with a higher Bishop score prior to induction, responded to single induction, and had a higher number of vaginal deliveries than those with lower vaginal pH. There was no significant association found in vaginal pH and the time taken to enter into active phase of labor. Subjects with pregnancy induced hypertension were found to have higher vaginal ph.
Conclusions: Parity influences vaginal pH and vaginal pH itself has a significant effect on the Bishop Score prior induction. Hence knowing the vaginal pH prior induction could be a useful tool to assess the labor outcome in induction with PGE_2.

Keywords: Vaginal pH, Labour induction, Dinoprostone gel (PGE_2)

INTRODUCTION

Induction of labour is defined as an intervention designed to artificially initiate uterine contractions leading to progressive dilatation and effacement of the cervix and birth of the baby. About 20% of pregnant women will have labour induced for a variety of reasons. There are various medical and surgical methods of Induction/Cervical ripening. Overall, induction of labour using prostaglandins seem to improve the rate of successful vaginal delivery, lower the rate of caesarean section, lower epidural usage and to be associated with improved maternal satisfaction.[1]

Cervical ripening is the process that culminates in the softening and distensibility of the cervix, which facilitates labor and delivery. The cervix contains relatively few smooth muscle cells and derives its rigidity from collagen bundles surrounded by proteoglycans. In pregnancy nearing term, there are various factors that induce certain changes in the cervix leading to cervical ripening. There are agents that can artificially induce these changes if it has not occurred. It is difficult to separate methods of cervical ripening and labor induction.[4]

Cervical ripening is associated with the disorganization of collagen bundles which is likely to be effected by collagenase. The active area of cervical tissue remodelling is at the internal OS. The collagenase found in the cervix has been identified as neutrophil derived and

the invading neutrophil plays an important role in the tissue rearrangements associated with cervical ripening. Neutrophils represent a readily available source of collagenase, present in specific granules, which can be made available by degranulation by a variety of cytokines including interleukin (IL-8). This dual action of IL-8, recruiting and exciting neutrophils, makes it a powerful agent in initiating rearrangement of extracellular matrix.[2,3]

Prostaglandin (PGE) is a well-established agent that has a primary action in softening the cervix. Compounds such as IL-8 act synergistically with PGE in attracting neutrophils.[2]

The human uterine cervix can produce nitric oxide (NO), a free radical with an ultra-short half-life. Nitric oxide in the human uterine cervix acts as an endogenous ripening factor with an unknown mechanism of action. In two studies conducted by Vaisanen-Tommiska M et al, it was found that cervical fluid nitric oxide metabolite level rises after cervical ripening, nitric oxide donor administration, or cervical manipulation, which supports a role for cervical nitric oxide in cervical ripening.[4,5]

Nitric oxide and PGE are the two pathways that, cross activating each other, trigger the cascade of events responsible of cervical ripening.

M. Norman et al studied the metabolism of cervical connective tissue in cervical biopsies from non-pregnant and pregnant cases. The concentration of proteoglycans in the pregnant cervix was found to be approximately one-half of that in the non-pregnant cervix indicating that the turnover of proteoglycans in pregnant cervical tissue was significantly increased. After prostaglandin induction it was found that the decrease in sulfated glycosaminoglycans could decrease electrostatic interactions that would weaken interfibrillar interactions that would be consistent with a decline in cervical resistance. The involvement of matrix metalloproteinases (MMP) i.e. MMP-2 and MMP-9 in the cervical ripening process has been indicated in cervical ripening.[6,7]

To summarize, the complex interactions of various cytokines bring about profound changes in the proteoglycans in the cervix which eventually leads to cervical ripening.

Recently, vaginal pH has been investigated as a potential factor influencing the efficacy of prostaglandins for cervical ripening and labor induction but the results have been conflicting. Studies have been conducted on the effects of vaginal pH on the efficacy of controlled-release PGE_2 vaginal insert and PGE_2 gel for cervical priming/labor induction in which overall vaginal pH seemed to influence the PGE_2 release.[9-11]

Nonetheless, the effect of vaginal pH on overall efficacy of the cervical ripening/labor induction with PGE_2 has not been well studied.

The vaginal pH in pregnancy is known to be acidic and not much is known about the variations in vaginal pH throughout pregnancy. There are studies that mention that pH may change the degree of ionization of a drug and affect the absorption of the drug resulting in variable clinical responses.[13,16]

Vaginal pH changes also has a role in preterm delivery which suggests that it has a role in influencing cervical ripening.[14,15]

The purpose of this study is to evaluate the influence of vaginal pH on the efficacy of PGE_2 gel for cervical ripening/labour induction which would improve patient selection for PGE_2 induction and reduce the incidence of failed induction with PGE_2.

METHODS

A prospective study was conducted on 200 subjects who were undergoing induction of labour with dinoprostone (PGE2) gel. All subjects had a medical or an obstetric indication for induction of labour. The study was conducted for a duration of 1 year at Lady Goschen Hospital, Mangalore,Karnataka,India approved by the ethics committee.

Inclusion criteria were: Unfavourable cervix, Singleton pregnancy with vertex presentation and no contraindication to vaginal delivery, Absence of spontaneous uterine contractions, Reactive NST.

Exclusion criteria included: Hypersensitivity to prostaglandins, Ruptured membranes, Chorioamnionitis, Previous LSCS.

Subjects who met the above mentioned criterias were enrolled in this study after giving an informed consent.

1. The vaginal pH of the subjects was assessed with pH indicator paper strips (pH paper, Sigma Chemical Company, St. Louis, USA) after performing cardiotocography to rule out uterine contractions and to assess fetal status.
2. Bishop score was assessed: Cervical dilatation, cervical effacement/length, Cervical consistency, Cervical position, Fetal station. Each component is given a score of 0-2 or 0-3. The highest possible score is 13 and <5 is unfavourable that needs induction.[1]
3. All received intracervically placed PGE2 gel 0.5 mg. After 6 hrs depending on Bishop Score and uterine contraction either PGE2 gel was repeated (maximum 3 doses) or labour was augmented as per labour theatre protocol.[1] The time taken to enter into active phase of labour was assessed.

4. The subjects were divided into two groups one with higher vaginal pH and the other with lower vaginal pH and the differences between the groups with respect to age, parity, Bishop score prior induction, need for a second induction, time to enter into active phase of labour and the final mode of delivery were compared and analysed.

A statistical package SPSS version 17.0 was used to do the analysis. The significance of association of each was calculated by Chi-square test. P value < 0.05 was considered significant.

RESULTS

Table 1: Comparison of vaginal pH and age.

pH	Age <25 year n=%	Age >=25 years n=%
<=4	92.9	7.1
4.5	83.3	16.7
5	97.1	2.9
5.5	88.7	11.3
>=6	82.1	17.9

Data as n=%.; *P value = 0.208

Table 2: Comparison of vaginal pH and time taken to enter active phase of labour.

pH	Time taken to enter active phase <12 hours n=%	Time taken to enter active phase >=12 hours n=%
<=4	83.3	16.7
4.5	57.1	42.9
5	66.7	33.3
5.5	70.8	29.2
>=6	85.5	14.5

Data as n=%.; *P value = 0.099

Table 3: Comparison of vaginal pH and various indications of LSCS.

pH	Failed induction n=%	Arrest of descent n=%		Non reassuring foetal status n=%	
<=4	62.5	4.2	33.3		
4.5	14.2		0	85.8	
5	11.2			33.3	55.5
5.5	12.5			50	37.5
>=6	37.5			12.5	50

Data as n=%.; *P value = 0.000

In this observational study, 200 subjects who were induced with prostaglandin gel were taken randomly. Vaginal pH was measured and compared with respective age, parity, Bishop Score prior induction, need for a repeat induction, time to enter active phase and the final mode of delivery.

Majority of the study subjects had pH in the range of 5-6 (Figure 1).

The vaginal pH in pregnancy is known to be acidic and not much is known about the variations in vaginal pH throughout pregnancy. In the present study most of the subjects were found to have pH between 5-6.

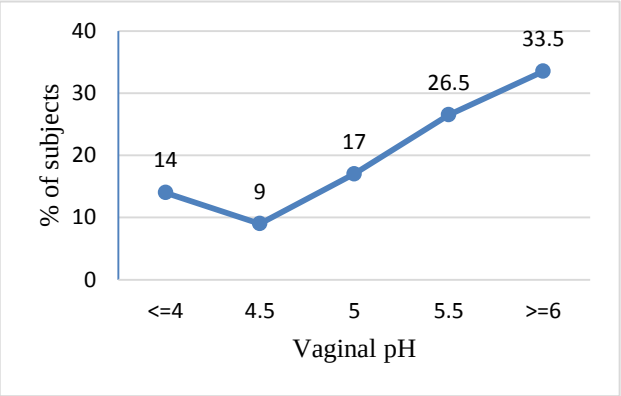

Figure 1: Vaginal pH among the study subjects. Majority of the study subjects had pH in the range of 5 – 6.

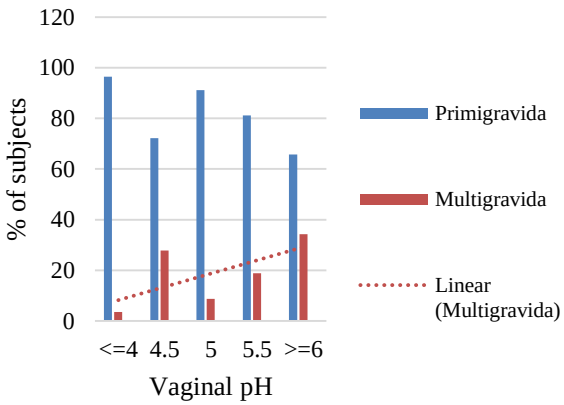

Figure 2: Comparison of vaginal pH with parity.

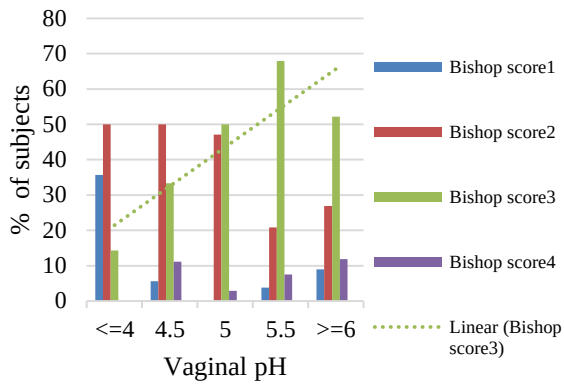

Figure 3: Comparison of vaginal pH and Bishop Score

There was no significant association found between vaginal pH and age of the subjects (Table 1). Although there was a significant association between vaginal pH and parity. Subjects of a higher parity had a higher vaginal pH (>=5) as depicted by the dotted lines which was statistically significant (P=0.003) (Figure 2).

Subjects with a higher vaginal pH (>=5) had higher Bishop Score (3, 4) as depicted by the dotted line which was statistically significant (P=0.000) (Figure 3).

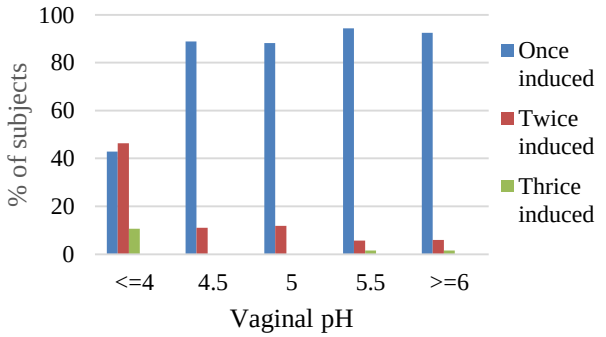

Figure 4: Comparison of vaginal pH and the number of times a subject was induced.

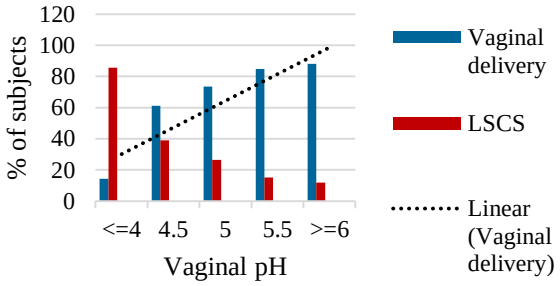

Figure 5: Graphical representation of vaginal pH and the delivery outcome.

Subjects with a higher vaginal pH (>=5) responded to a single induction while subjects with lower vaginal pH needed a repeat induction (maximum of three doses in an interval of 6 hours) which was statistically significant (P=0.000) (Figure 4).

There was no significant association found in vaginal pH influencing the time taken to enter active phase of labor (Table 2).

Subjects with higher vaginal pH (>=5) was associated with more number of vaginal deliveries and subjects with lower vaginal pH was associated with more number of LSCS as depicted by the dotted lines which was statistically significant (P=0.000) (Figure 5).

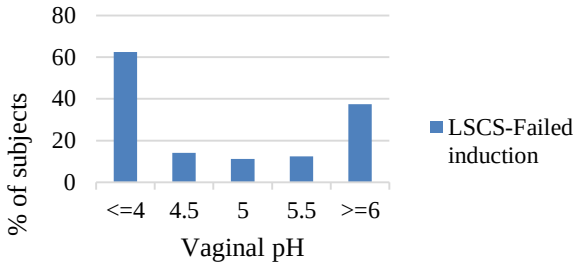

Figure 6: The number of subjects who went for LSCS with failed induction as the indication of LSCS.

Most of the subjects who underwent LSCS for failed induction being the indication for LSCS had a lower vaginal pH (Table 3/Figure 6).

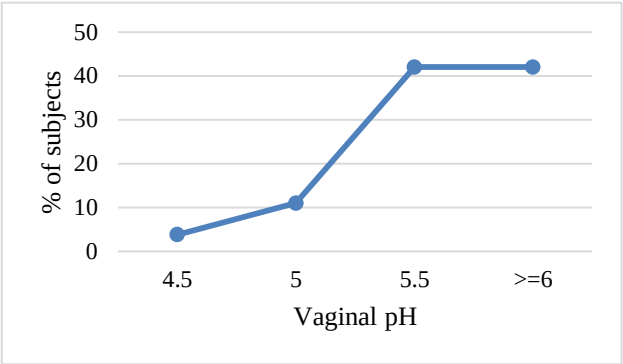

Figure 7: Graphical representation of comparison of vaginal pH in subjects with pregnancy induced hypertension.

Subjects with pregnancy induced hypertension were found to have higher vaginal pH (Figure 7).

DISCUSSION

Among the previous studies in the literature; there are three studies investigating the effect of vaginal pH on efficacy of PGE2 gel and the another three investigating the effect of vaginal pH on the efficacy of slow-release PGE2 vaginal insert in vivo but giving conflicting results.[8-11,17,18]

The first study was carried out in 2001 by Lyrenas et al, who evaluated the effect of vaginal pH and efficacy of a controlled-release PGE_2 vaginal insert in 68 subjects with an unfavourable cervix who were undergoing labor induction and the investigators noted a significant correlation between vaginal pH and PGE_2 release from the insert.[10]

Ramsey et al studies conducted in 2002 and 2003 conflict each other.[8,9] The study in 2002 conducted with PGE_2 gel showed significant association between higher vaginal pH and the shorter time taken to enter into active phase, time to full dilatation and time to delivery while the study in 2003 conducted with PGE_2 vaginal insert showed no

significance. The present study also showed no significant change in the time to enter active phase of labor.

In the present study conducted there was a significant association found between the vaginal pH and the Bishop score prior induction but the change in the Bishop score over 6-8 hours of induction could not be assessed. In the studies conducted by Ramsey et al and Basirat et al, there was no significant association found between vaginal pH and the initial Bishop score prior induction and the change in the Bishop score over 12 hours in contrast to the study conducted by Singh u et al where there was significant association found between the vaginal pH and the change in the Bishop score over 18 hours which may be due to the difference in the duration (in hours) of assessment of Bishop score after an induction.

Table 4: Summary of comparison of the present study with previous conducted studies.

Year of study	Study conducted by	PGE2 form used in study	Number of subjects in study	Association of vaginal pH and AGE	Association of vaginal pH and PARITY	Association of vaginal pH and Bishop score prior induction	Association of vaginal pH and time to enter active phase
2002	Ramsey et al	Gel	32	a	a	a	b
2003	Ramsey et al	Insert	34	a	a	a	a
2008	Onen et al	Insert	63	a	a	a	a
2011	Singh U et al	Gel	45	a	a	a	a
2012	Basirat et al	Gel	147	a	a	a	b
	Present study	Gel	200	a	b	b	a

a- Significant association; b- No significant association

Basirat et al also found that the incidence of Cesarean section was lower in women with high vaginal pH as in the present study but was not statistically significant.

Vaginal pH has been investigated in several recent studies as a factor that may account for the variability observed clinically with prostaglandin used as cervical ripening/labor induction agents. Two in vitro studies by Johnson et al. and MacDonald and Weir describes an increased PGE_2 release in solutions with a higher pH. (6.5 to 7.5) It was also reported in the two in vitro studies that along with the increased release of PGE_2, it is also predominantly ionized at a pH of 7.5 (pKa, 4.9), which diminishes the potential of its systemic absorption.[13,16]

Lyrenas et al further noted that high vaginal pH (6.5-7.5) and therefore increased PGE_2 release did not equate to increased plasma concentrations of PGE_2 and its metabolites. Therefore, why vaginal pH affected the cervical priming but did not affect the labor outcomes in present study may be due to these findings that ionization of PGE_2 in high pH might cause local effects, like change in Bishop's score, and the diminishing of its absorption may decrease its systemic effects and therefore, absence of change in labor outcome.[11]

An important observation made in the present study was that subjects with pregnancy induced hypertension were found to have a higher vaginal pH (Figure 7). Hence this observation could probably explain on why subjects with pregnancy induced hypertension respond well to PGE_2 induction and further studies are required to substantiate its significance.

The pH is important in terms of the design and the efficacy of vaginal drug delivery systems. The effect of vaginal pH on the efficacy of sustained-release PGE vaginal insert could be better established if the vaginal insert had been moistened with solutions having different pH as in the previous studies.[19]

CONCLUSION

Hence, findings of the present study suggest that parity influences vaginal pH and vaginal pH itself has a significant effect on cervical ripening and the Bishop Score prior induction. Higher vaginal pH more often responds to a single induction and is more often associated with vaginal deliveries than LSCS.

Hence knowing the vaginal pH prior induction could prove to be a useful tool in assessing the labor outcome of a patient undergoing labor induction with PGE2 gel. Further research is required to find various agents that would increase the vaginal pH thereby creating a favorable environment for PGE2 gel induction.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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